REMARKS

This Amendment and Response is filed following receipt of the second Office Action, made Final in the present application, mailed November 12, 2003, and subsequent to an in-person interview with the Examiner on March 10, 2004 (summarized below). Applicants acknowledge that the Examiner has withdrawn the previous objections to the specification and abstract, and the previous restriction requirement. Applicants also acknowledge that claims 19, 21, 22, and 34-38 have been withdrawn from consideration; these claims have presently been cancelled, as required by 37 C.F.R. §1.113(c). Claim 39 has also been voluntarily cancelled, presently. Upon entry of the present amendments, claims 28-33 are pending. The subject matter of these claims is believed to be in condition for immediate allowance.

Claim 39 (drawn to a phosphothreonine-specific context-independent antibody) has been voluntarily cancelled in order to expedite prosecution and allowance of the preferred subject matter of claims 28-33. Applicants reserve the right to pursue the subject matter of cancelled claim 39, as well as other cancelled claims, in a co-pending or subsequent application.

Claim 28 (drawn to a preferred genus/class of motif-specific, context-independent antibodies provided by the invention) has been voluntarily amended to further point out the features and characteristics of the claimed genus of antibodies. Namely, an antibody within the genus has the following characteristics: (i) it "specifically" binds a "recurring" phosphorylated kinase consensus substrate or protein-protein binding motif; (ii) the motif for which the antibody is specific "consists of up to four invariant amino acids" as well as at least one phosphorylated amino acid, and may further include "optionally, one or more variable/degenerate amino acid positions"; and, (iii) the antibody "specifically" bind the motif in multiple "different" peptides or proteins "from an organism in which said motif recurs." Claim 28 has also further been voluntarily amended to expressly recite a distinction made clear in the specification, namely, that an antibody within the claimed genus is "not a site-specific antibody" of the type known in the prior art (the limitations of which have been discussed in the specification and during prosecution). Support for these amendments is found throughout the specification and claims as originally filed, *e.g.* at p. 5, lines 4-15; p. 7, lines 5-27; p. 8, lines 5-14; p. 18-19; p. 19-23, generally, p.24, lines 15-27; and the exemplary species of the genus that described in Examples II-IV and VI-VIII. The present amendments to claim 28 also address the Examiner's request that Applicants reword the previously used phrase "within a genome." These amendments do not introduce new matter.

Dependent claim 29, which is drawn to preferred species of antibodies within the genus of claim 28, has been voluntarily amended to further include the amino acid sequence of each motif after the name

of each preferred kinase consensus substrate motif or protein-protein binding motif. Support for these amendments is found throughout the specification and claims as originally filed, *e.g.* in Examples II-IV and VI-VIII. These amendments do not introduce new matter.

Dependent claim 32 has been voluntarily amended to eliminate a phrase, in step (c), regarding the context-independent features of antibodies within the claimed genus, which phrase unnecessarily duplicates a similar limitation already present in claim 28, from which claim 32 depends.

Applicants submit that all of the outstanding concerns and rejections raised by the Examiner have presently been addressed and overcome (as set forth in detail below), and respectfully request that the pending claims, as amended, be promptly advanced to allowance and issuance.

Summary of Interview:

Applicants' attorney (Mr. James G. Cullem, Esq.) along with Dr. Roberto Polakiewicz, Ph.D. (a scientist of ordinary skill in the art of antibody production and use, including phospho-specific and anti-peptide antibodies) met with the Examiner on March 10, 2004, in order to discuss the outstanding rejections in the present case. Mr. Cullem and Dr. Polakiewicz discussed with the Examiner how the features and characteristics of the presently claimed class of motif-specific antibodies differ from those of prior art, traditional "site-specific" antibodies. Also discussed were the grounds on which the Examiner believes the written description rejection (outstanding) was supportable and appropriate, and Applicants' reasons for why the rejection is inappropriate and not supportable on the law and facts in the record.

Specifically, the Examiner's attention was drawn to the fact that written description must be assessed from the eyes of those skilled in the relevant art, and that in arts where the level of skill is high (as here), the required level of detail in the description is lower. Mr. Cullem and Dr. Polakiewicz specifically discussed with the Examiner evidence establishing the very high level of skill and knowledge in the art of antibodies (including anti-peptide antibodies and their production), to which the present invention pertains. Also discussed were the USPTO's and Federal Circuit's own recognition of the high level of skill in this art, and that written description for antibodies may be established in a variety of ways, including by reduction to practice of adequate representative species, description of binding characteristics and features, etc. Mr. Cullem reminded that Examiner that she may not supplant the view of those of skill in the art with her own opinion (*i.e.* an examiner is *not* the ordinarily skilled artisan for purposes of assessing written description), but rather must view the description and invention *as those of skill in this art would view it*, from their base of knowledge. The Examiner was also reminded that she may not make a mere allegation that written description is simply "inadequate" or that an art is

"unpredictable" but is instead required to proffer evidence to support such allegations, and that absent sufficient supporting evidence, the present written description must be taken as sufficient.

The Examiner, having argued in the outstanding Office Action that antibody production in accordance with the present invention was unpredictable, conceded that the level of knowledge and skill in this art is high. However, the Examiner continued to assert that although that level of skill is antibodies is high, the modified antibody production technique described in the instant application was not, and was somehow therefore unpredictable. Mr. Cullem and Dr. Polakiewicz maintained that this was not the case given the high level of skill of the art and well-established anti-peptide and phospho-specific antibody production and screening techniques, over which the present invention improves.

Also specifically discussed were the Examiner's basis for arguing that the presently claimed genus of antibodies lack sufficient written description. The Examiner argued that Applicants had not described a sufficient number of species within the genus, and are only entitled to the species actually reduced to practice. Mr. Cullem disagreed and reminded the Examiner that both the USPTO and Federal Circuit have made clear that support for a genus does *not* require literal description of every species within the genus, but rather possession of the genus can be shown by describing the essential features/characteristics of species within it, as well as actual reduction to practice of a number of species that are representative of the variation within the genus. Mr. Cullem and Dr. Polakiewicz explained to the Examiner that the subject matter as presently claimed and described (including reduction to practice of six species representative of variation within the genus) satisfies written description when viewed, as required, from the eyes of those of skill in the art of antibodies. Applicants also discussed the knowledge in the art of the common structural features of recurring phosphorylated kinase consensus substrate motifs and protein-protein binding motifs to which the invention pertains. Mr. Cullem reminded the Examiner that, again, she could not base the present rejection on a mere allegation that the species described were "not enough," but must proffer evidence to support her position and must consider number of species as but one factor in the multi-factor written description assessment.

Upon conclusion of the interview, Mr. Cullem informed the Examiner that this Response would be accompanied by a Declaration by Dr. Polakiewicz in support of the present application, in which various references establishing the high level of knowledge and skill in this art, and establishing that the exemplary species described in the application are representative of the claimed genus, would be discussed. The Examiner agreed to reconsider her position on written description following filing of this Response and the supporting Declaration.

I. NEW REJECTIONS OF CLAIM 39.

§112, 1ST PARAGRAPH, WRITTEN DESCRIPTION REJECTION
§112, 2ND PARAGRAPH, INDEFINITENESS REJECTION
§102(E) REJECTION

The Examiner has rejected claim 39 under (i) 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not adequately described in the specification, (ii) 35 U.S.C. §112, second paragraph, as allegedly being indefinite, and (iii) 35 U.S.C. §102(e), as allegedly being anticipated by Tani *et al.*, U.S. Patent No. 6,001,580 (previously cited by the Examiner in the last Office Action).

These rejections are now moot, since Applicants have presently canceled claim 39 in order to expedite prosecution and allowance of the preferred subject matter of claims 28-33. Accordingly, Applicants request the rejections be withdrawn.[1]

II. MAINTAINED CLAIM REJECTIONS.

§112, 1ST PARAGRAPH, WRITTEN DESCRIPTION REJECTIONS

The Examiner has maintained the rejection of claims 28-33 under 35 U.S.C. §112, first paragraph, as allegedly claiming subject matter not adequately described in the specification. The Examiner premises the maintained written description rejections on four generalized assertions:

(i) that "raising or producing the claimed antibodies is not well known and is very unpredictable according to the background section of the specification," which assertion is predicated on a single prior art attempt to make phosphothreonine-specific antibodies as described and distinguished in the Background of the specification (*See* November 12, 2003 Office Action at p. 9, lines 10-15);

(ii) that "the disclosed antibodies which bind to the [representative motifs of the Examples] do not

---

[1] Nonetheless, Applicants wish to note a few points. The subject of matter of claim 39 is a preferred species of disclosed antibody that specifically binds a *single* phosphothreonine residue, and binds it in multiple different proteins or peptides in which it occurs. The binding specificity and characteristics of this antibody recited in the claim are thus clear and definite to those of skill in the art of antibody production and use. This antibody was *actually reduced to practice*, and its production, binding specificity and characteristics are described in great detail in the specification in Example 1 (pages 27-35). Thus, the specification more than adequately describes the claimed antibody since it would exceedingly apparent to one of skill in the art that the inventors were in possession of an antibody they in fact actually produced and characterized in detail. Lastly, Tani (the '580 patent) does *not* disclose an antibody that is specific for a single phosphothreonine residue. Rather, it is an ERK1/2 phosphorylation site-specific antibody that binds a 12-residue long epitope. Thus, the '580 patent in no way anticipates the antibody of claim 39 because it fails to teach each and every limitation of the claim. Accordingly, the rejections are not proper. Nonetheless, Applicants have presently cancelled the claim 39 solely to advance allowance of the preferred subject matter of claims 28-33.

represent the genus as claimed," which assertion the Examiner predicates on the Federal Circuit's holding in *Eli Lilly* that "For inventions in an unpredictable art, adequate written description of genus embracing widely variant species can not be achieved by disclosing only one species within the genus" (*See* November 12, 2003 Office Action a p. 9, lines 1-7, citing *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559 (1997), discussed at MPEP §2163);

(iii) that "in the absence of sufficient teaching in the specification by structure or drawing showing the antibodies of the claimed invention" possession of the claimed genus of antibodies has not been shown, which assertion the Examiner predicates on the Federal Circuit's holding in *Vas Cath* (*See* November 12, 2003 Office Action at p. 9, lines 15-18, citing *Vas Cath Inc. v. Mahurkar*, 935 F.2d 1555 (1991), discussed at MPEP §2163); and

(iv) that "for inventions in emerging and unpredictable technologies, disclosure of only a method of making the invention and the function may not be sufficient to support a product claim," which assertion the Examiner predicates on the Federal Circuit's holding in *Fiers* (*See* November 12, 2003 Office Action at p. 10, lines 5-8, citing *Fiers v. Revel*, 984 F.2d 1164 (1991), discussed at MPEP §2163).

Upon these generalized premises the Examiner asserts that one of skill in the art would not recognize that the inventors were in possession of the claimed genus of antibodies as of the filing date of the application. The Examiner's summary conclusion that the claimed subject matter relates to an unpredictable art is fundamentally flawed, and the rejection not supported by law (including the cases relied on) or the evidence in this case. Accordingly, Applicants traverse the rejection.

Firstly, the Examiner has erred in summarily concluding, despite the weight of evidence to the contrary, that the art to which the invention pertains is somehow unpredictable and not mature. As discussed below, the evidence of record, including published scientific literature, Federal Circuit decisions, the USPTO's own Guidelines, and the Declaration of a skilled artisan enclosed herewith, all indicate the mature and predictable nature of the art of antibody production and characterization, to which the present invention pertains. The Examiner has further erred in misapplying certain Federal Circuit decisions respecting the written description requirement to the particular invention and technology at issue in *this* case, namely, antibodies and their production and use. Under the controlling written description standards, as further discussed below, the Examiner has erred in concluding that one of ordinary skill in this advanced art would not recognize possession of the presently claimed genus of antibodies in view of the detailed description provided in the specification, and the rejections are therefore improper and should be withdrawn.

A. The Examiner has Failed to Assess the Disclosure from the Standpoint of One Skilled in the Art of Antibodies, their Production and Use, which the Evidence of Record Indicates is a Mature Art with a High Level of Skill.

To satisfy the written description requirement, a specification must convey to one of skill in the art to which the invention pertains that the inventors were in possession of the claimed invention at the time of filing. *See* MPEP §2163(3)[a], *citing Purdue Pharma L.P. v. Faulding* (Fed. Cir. 2000); *see also* MPEP §2163.02. Stated a different way, the test is whether one of skill in the art (*not* an examiner) would recognize, based on the disclosure, that the inventors invented the subject matter now claimed. *See, e.g. Gentry Galley v. Berkline Corp.*, 134 F.3d 1473 (Fed. Cir. 1998), *citing In re Gostelli* (Fed Cir. 1989)).

In assessing whether adequate written description is provided in the specification, an examiner must view the disclosure from the standpoint of one skilled in the relevant art, giving due weight to the level of skill and knowledge in that art, and the level of advancement of the art. Indeed, the MPEP states "Such a review is conducted from the standpoint of one of skill in the art . . . and should include a determination of the field of the invention and the level of skill and knowledge in the art." §2163(II)(A)(2), *citing Wang Labs v. Toshiba Corp.*, 993 F.2d 858 (Fed. Cir. 1993).

The level of knowledge in, and state of, the relevant art is so important to the assessment of possession that the MPEP instructs:

> "Patents and printed publications in the art should be relied upon to determine whether an art is mature and what the level of knowledge and skill is in the art. In most technologies which are mature, and wherein the knowledge and level of skill in the art is high, a written description question should not be raised for original claims even if the specification disclosed only a method of making the invention and the function of the invention." §2163(II)(A)(3), *citing in re Hayes Microcomputer Products, Inc. Patent Litigation, 982* F.2d at 1527 (Fed. Cir. 1992).

In the present case, the evidence or record indicates that the art to which the invention relates – the art of antibodies, their production, characterization, and use – is a mature art, where the level of skill and knowledge is very high. Accordingly, the advanced state of this art strongly supports the sufficiency of the written description of the invention provided by the inventors.

The presently-claimed invention is a genus of antibodies with the following identifying characteristics: (i) the antibodies specifically bind a recurring kinase consensus substrate motif or protein-protein binding motif, (ii) the motif bound by the antibodies contains at least one phosphorylated amino acid and up to four invariant amino acids, as well as, optionally, one or more variable/degenerate

amino acid positions, and (iii) the antibodies bind their target motif in multiple different peptides or proteins in which the motif recurs. The specification describes these antibodies, their production, characterization, and use. Accordingly, the art to which the invention pertains, in its broadest sense, is antibodies, their production, characterization, and use, and more particularly, to anti-peptide antibodies (i.e. antibodies raised against synthetic peptide antigens).

The art of antibodies, and their production and characterization, has been recognized as a mature art, where the level of skill and knowledge is very high. The structure and function of antibodies, and the correlation between the two, is well known. For example, the USPTO itself, in its Revised Interim Written Description Guidelines (http://www.uspto.gov/web/ patents/ guides.htm), discusses written description requirements pertaining to exemplary antibody claims and technology, and clearly states:

> "The general knowledge in the art is such that antibodies are structurally well characterized. It is well known that all mammals produces antibodies and that they exist in five isotypes, IgM, IgG, IgD, IgA, and IgE. Antibodies contain an effector portion which is the constant region and a variable region that contains the antigen binding sites in the form of complementary determining regions and the framework regions. The sequences of constant regions as well as the variable region subgroups (framework regions) from a variety of species are known and published in the art. It is also well known that antibodies can be made against virtually any protein.
>
> ***
>
> *This is a mature technology where the level of skill is high and advanced.*
>
> ***
>
> Considering the routine art-recognized method of making antibodies to fully characterized antigens, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that *the antibody technology is well developed and mature*, one of skill in the art would have recognized that the spectrum of antibodies which bind to [hypothetical] antigen X were implicitly disclosed as a result of the isolation of antigen X." *See* Written Description Guidelines, *supra.* at p. 59-60 (emphasis added).[2]

The Federal Circuit, in favorably commenting on the USPTO's Guidelines, has also

---

[2] Note the PTO's recognition that a spectrum of antibodies that bind a desired antigen are *implicitly* disclosed once the antigen is described; not merely a *single* antibody. In other words, because the level of skill and knowledge in this art are so high, once an artisan knows the antigen against which they would like to produce an antibody, and antibody specifically binding it can be readily produced and used. This is consistent with the PTO's regular issuance of broad antibody patents to a disclosed protein sequence, even though no such antibody was actually reduced to practice and specific antigenic sequences within the protein sequence have *not* be described or disclosed.

acknowledged the mature nature of the antibody art and the high level of skill and knowledge in this art. In *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, the Federal Circuit, in distinguishing the type of written description required to show possession of DNA molecules from that required to show possession of other biological molecules, stated:

> "For example, the PTO would find compliance [with the written description requirement] for a claim to an isolated antibody capable of binding to antigen X, *notwithstanding the functional definition of the antibody*, in light of the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that antibody technology is well developed and mature." *Enzo Biochem*, 296 F.3d 1316 (Fed. Cir. 2002), *citing the* USPTO Written Description Guidelines (emphasis added).

The *Enzo* court then went on to state its agreement with, and adoption of, the PTO's approach to assessing adequate written description in well developed arts with a high level of skill, where a known correlation between structure and function exists, such as with antibody production. Other Federal Circuit decisions have also recognized the mature nature of antibody production, characterization and use, and the high level of skill in this art. *See, e.g. Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). The PTO Board of Patent Appeals has also recognized the mature nature of this art. *See, e.g. Ex Parte D*, 27 USPQ2d 1067 (BPAI 1993).

The scientific literature and several well-known and standard references in this art also clearly evidence the advanced state of antibody production, characterization, and use, and the high level of knowledge and skill in this art. For example, an entire seven hundred page manual, ANTIBODIES: A LABORATORY MANUAL, Harlow & Lane (1988), Cold Spring Harbor Laboratory, is devoted solely to the production, characterization, and use of antibodies. Three detailed chapters alone are dedicated to the structure, features, and characteristics of antibodies and their binding. Another, four detailed chapters are dedicated to the production and screening of antibodies – including anti-peptide antibodies -- while six more detailed chapters are dedicated to the use of antibodies. This manual is widely known and used by those of skill in this art and its techniques are considered standard. *See* Polakiewicz Declaration at ¶9. Another widely-known and standard reference in this art is CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, Volume 2, John Wiley & Sons (1992), which devotes over 102 pages, in Section 11, solely to the production, characterization, and use of antibodies, including anti-peptide antibodies.[3] This manual is also widely known and used by those of skill in this art and its techniques are considered standard. *See*

[3] And another entire 400-plus page text, MONOCLONAL ANTIBODIES, Peters & Baumgarten, Eds., Springer Laboratory (1992) is dedicated solely to the production, characterization, and use of monoclonal antibodies.

Polakiewicz Declaration at ¶9. Both of these detailed technical references, which Applicants previously cited, underscore the advanced nature of this mature art, and the high level of skill and knowledge in antibodies, their features, production, characterization, and use.

Other well-known technical references in this art further underscore the mature nature of, and advanced level of skill in, this art. For example, Czernik *et al.*, METHODS IN ENZYMOLOGY *201:* 264-283 (1991) and Czernik *et al.*, *Neuroprotocols 6:* 56-61 (1995) described and established the standard technique for producing, screening, and characterizing phosphorylation site-specific antibodies using synthetic peptide antigens. The general technique first described in Czernik has been practiced for more than a decade, and remains widely practiced today as the standard anti-peptide phospho-antibody production methodology. *See* Polakiewicz Declaration at ¶9. Later improvements in the standard technique for anti-peptide antibody production and characterization described in Czernik became part of the standard methodology at the time the present application was filed. For example, Bangalore/Stern *et al. Proc. Natl. Acad. Sci. 89:* 11637-11641 (1992) and Epstein *et al.*, U.S. Patent Number 5,599,681, "Activation State-Specific Phosphoprotein Immunodetection," Issued Feb. 4, 1997, each describe general production methodologies employing chemically (rather than enzymatically) phosphorylated amino acid residues in synthetic peptide antigens according to the standard methodology set forth by Czernik. *See* Polakiewicz Declaration at ¶10. This practice became the standard anti-phosphopeptide antibody production technique, both at the time the present application was filed and to this day. *See Id.* In fact, this is the methodology generally followed by Applicants, but with an important and novel modification leading to the present invention. *See Id.* at ¶10. Indeed, the number of scientific literature references describing the use of phospho-peptide antigens in the standard methodology to produce phosphorylation site-specific antibodies is too numerable to list here. The exemplary disclosures of Czernik, Bangalore/Stern, and Epstein, all previously cited by Applicant, further establish the mature and advanced state of antibody production, including anti-peptide antibodies, to which the invention relates.

Accordingly, the evidence of record clearly indicates that the art of antibody production, characterization, and use -- including anti-peptide antibodies – to which the invention relates is mature and advanced, with a high level of skill and knowledge. The Examiner has, therefore, failed to assess the present specification from the standpoint of one skilled and knowledgeable in this mature and advanced art and improperly maintained the present written description rejection. *See* MPEP §2163(II)(A)(3), *citing Hayes Microcomputer 982* F.2d at 1527. One of ordinary skill in this mature art would recognize, based on Applicants' disclosure (which teaches the production, characterization, and use of a novel class

of anti-peptide antibodies) possession of the claimed class of antibodies.[4] *See* Polakiewicz Declaration at ¶17, 18. Accordingly, the specification satisfies the written description requirement and the outstanding rejection of claims 28-33 should be withdrawn.

B. The Examiner's Assertion that the Production of Antibodies is Unpredictable is not Supported by any Evidence of Record, nor is the Single Factor of Predictability Sufficient to Assess Possession.

As noted above, the assessment of adequate written description is *not* a single, simple determination, but rather a factual determination to be reached by considering a number of factors. MPEP §2163(II)(A)(3), *citing Eli Lilly*, 119 F.3d at 1568. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. *See Id.* Although predictability of the relevant art may be a factor to be considered in assessing whether possession of a claimed genus is achieved by disclosure of one or few species, it is but one factor among many to be considered and does *not*, alone, control the adequacy of written description.[5] *See Id.*

Indeed, the Federal Circuit and MPEP have clearly mandated that if one of skill in the relevant art can readily discern the features and characteristics of the claimed invention, given the level of skill and knowledge in their art, then possession has been established, regardless of whether the art is unpredictable. *See* MPEP §2163(II)(A)(2), *citing, e.g. Wang Labs.*, 993 F.2d 858. Accordingly, *even if* the art of antibody production, characterization, and use were unpredictable, the Examiner has erred by relying upon this single factor in assessing whether Applicants' specification has established possession of the claimed genus of antibodies in the eyes of those skilled in this art. The Examiner *must* give due

---

[4] "Possession" of a claimed invention for purposes of satisfying the written description requirement of 35 U.S.C. 112, 1st paragraph, is shown by describing, in the specification, the claimed invention with all of its limitations. *See* MPEP §2163(I), *citing Lockwood v. American Airlines,* 107 F.3d 1565 (Fed. Cir. 1997).

[5] On this point, the Federal Circuit has stated (in considering claims to DNA lacking sequence actual information) that written description "fails *not merely* because the field is unpredictable, or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to the factual uncertainty [about actual sequence] that undermines the specificity of the inventor." *Burroughs Wellcome Co. v. Barr Laboratories Inc.*, 40 F.3d 1223, 1229 (Fed. Cir. 1994), *cited at* MPEP §2163(II)(A)(3). In *Burroughs* the Federal Circuit made clear that uncertainty of a relevant art is, itself, not fatal to adequate written description. Rather, the DNA claim under consideration in *Burroughs* lacked supporting written description because the inventors did not have a completed conception of the identifying characteristics of their invention (namely, they did not know the sequence) and hence could not possible be in possession of it. This is in stark contrast to antibodies, the possession of which one establishes by defining binding and specificity characteristics, as Applicant has done in the present case.

consideration to the mature art of antibody production and the high level of skill and knowledge in this art, as well as the recognized correlation between structure and function of antibodies, etc. MPEP §2163(II)(A)(3), *citing Eli Lilly*, 119 F.3d at 1568; see also *Enzo Biochem*, 296 F.3d 1316; USPTO Written Description Guidelines, *supra.* The outstanding written description rejection of claims 28-32 based upon this single factor is therefore improper and should be withdrawn.

Moreover, there is no factual support for the generalized assertion that the art of antibody production, characterization, and use is unpredictable. To the contrary, the evidence of record in this case (including that discussed above), indicates that the antibody art to which the invention pertains is mature and predictable. An assessment of the state of the art, including whether it is predictable, must be based on factual evidence in the record, including printed publications. MPEP §2163(II)(A)(3), *citing Hayes Microcomputer*, 982 F.2d at 1527. Indeed, the MPEP clearly instructs:

> "A general allegation of 'unpredictability in the art' is not a sufficient reason to *make or support* a written description rejection." MPEP §2163.04(I) (emphasis added).

As discussed above, both the USPTO and the Federal Circuit have recognized the mature state of antibody production, high level of skill and knowledge in this art, well characterized functional attributes of antibodies, recognized correlation between structure and function of antibodies, and fact that antibodies can be made to virtually any desired target. *See* USPTO Guidelines, *supra.*; *Enzo Biochem*, 296 F.3d 1316. Inherent in this recognition is that the art of antibody production, characterization, and use is predictable, since the skilled artisan can readily produce an antibody with desired epitope specificity and binding characteristics to essentially any desired target. Indeed, in *Enzo Biochem*, the Federal Circuit noted that written description for an antibody would be satisfied "notwithstanding the functional definition of the antibody" because of the well defined structural and functional attributes of antibodies together with the mature state of the art. In other words, given the high level of skill and knowledge in the art, including well defined structural and functional features of antibodies, there is predictability in the art of antibody production, characterization, and use.

The scientific literature of record in this case also underscores the predictable nature of antibody production, characterization, and use, including production of anti-peptide phospho-specific antibodies, such as those of the present invention. As discussed above, several detailed and well-known technical references provide standard protocols for producing and characterizing antibodies – including anti-peptide antibodies – with desired specificity and binding characteristics. *See* ANTIBODIES: A LABORATORY MANUAL; CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, Volume 2; Czernik, METHODS IN ENZYMOLOGY; Epstein, U.S. Patent Number 5,599,681, *supra.* All of these references provide detailed

guidance for how to design or choose an epitope, generate an immune response and antibodies against the epitope, screen for and select antibodies with the desired specificity and binding qualities, and use isolated antibodies in standard immunological methods. As noted in the USPTO Guidelines and Federal Circuit decisions like *Enzo Biochem* and *Hybritech*, the production of antibodies has largely become routine to those of skill in this art. *See* Polakiewicz Declaration at ¶11. A scientist skilled in techniques of antibody production and characterization and can readily produce an antibody with the desired epitope specificity and binding characteristics according to standard methodologies well known in this mature art. *See* Polakiewicz Declaration at ¶11.

The predictability of antibody production, characterization, and use is also reflected in Applicants' specification. The specification provides *eight* working examples of context-independent antibodies produced accordingly to the disclosed methodology. All eight exemplary antibodies disclosed in the specification possess the desired characteristics of specificity for the target motif and context-independent binding characteristics. The production methodology described in the specification essentially follows the proven, predictable, and standard anti-peptide antibody production and characterization method known in the art (*see* Czernik, etc. *supra.*), but with a novel and important modification to the peptide antigen employed. *See* Polakiewicz Declaration at ¶9, 12. Those of skill in art of antibody production recognize, in Applicants' disclosure, a detailed written description of how to produce, characterize, and use the claimed class of antibodies, the production of which is both reproducible and predictable given the advanced state of the art and eight working examples provided in the specification.[6] *See* Polakiewicz Declaration at ¶16, 17.

The predictability of producing motif-specific, context-independent antibodies as disclosed in the specification is further evidenced by the nearly perfect success rate of antibodies produced by Applicants according to the disclosed methodology. Indeed, CELL SIGNALING TECHNOLOGY, INC., the assignee of the instant application, has to date produced over 20 different motif-specific, context-independent antibodies according to the specification, including antibodies specific for at least 16 different phosphorylated kinase consensus substrate motifs and protein-protein binding motifs. Only a single attempt did not yield an antibody with the desired characteristics of motif-specificity and context-independence. *See* Polakiewicz Declaration at ¶17. Many of these antibodies are listed for sale in CELL SIGNALING TECHNOLOGY'S 2003-04 Catalogue (at page 14). This high success rate further indicates, to

[6] Indeed, the Examiner herself has previously acknowledged this by allowing Applicants' production methodology in the parent of this case (now issued as U.S. Patent No. 6,441,140).

those of skill in this art, the predictability and reproducibility of producing the claimed antibodies in accordance with the teachings of the specification. *See* Polakiewicz Declaration at ¶17, 8.

Although the weight of evidence of record clearly indicates the art of antibody production, to which the invention relates, is predictable and mature, the Examiner nonetheless argues to the contrary that a single prior art failure (Heffetz *et al.*, *Meth. Enzymol. 201:* 44 (1991) – which was discussed and distinguished by Applicant in the Background of the specification – somehow establishes that the entire art is unpredictable. This assertion is legally and factually unsupportable. A single publication reporting a single failed scientific attempt does not outweigh the clear body of evidence, discussed above, indicating that the art of antibody production is advanced and predictable. Indeed, both the USPTO and Federal Circuit have recognized that those of skill in this art can readily produce a desired antibody to essentially any target, despite that fact that, as with all sciences, a given attempt may from time-to-time fail. Individual failures do not render an entire art unpredictable. The single failed attempt reported in Heffetz does not render the entire art of antibody production unpredictable.

Moreover, the particular production technique employed by Heffetz in their failed attempt to produce an antibody specific for a single phosphothreonine residue is readily distinguished from the proven production technique roughly followed by the present inventors and described in the specification. Heffetz reports an attempt to produce a phosphothreonine-specific antibody by coupling a phosphothreonine residue to a standard carrier protein, keyhole limit hemocyanin (KLH), in the hopes of raising an immune response directed only to the phosphoresidue. *See* Heffetz *et al.*, *Method. Enzymology 201:* 44 (1991), cited in the specification on page 5. The failure of their attempt was not surprising, since it is well known in the art that coupling a small chemical entity (a hapten) to a carrier, like KLH, may not necessarily produce antibodies against the small chemical entity. If the hapten is too small it may not be immunogenic enough to generate the desired immune response. *See* Polakiewicz Declaration at ¶21. Heffetz itself attributed their failure to this fact (contrasting their failure with the previous success of the hapten-carrier approach for generating an antibody specific for the larger and more immunogenic phosphotyrosine moiety).[7]

In contrast, the claimed class of motif-specific, context-independent antibodies described in detail in the specification were *not* produced by the hapten-carrier technique, but rather by the time-tested, proven, and distinct anti-peptide production approach (as modified by Applicants). As discussed at length above, the anti-peptide production technique, which employs synthetic peptide antigens to generate

[7] Of further note, Heffetz is absolutely irrelevant to the production of antibodies against multi-residue motifs, such as kinase consensus substrate motifs and protein-protein binding motifs, to which the present claims relate.

an immune response, has proven highly suitable and reproducible for production of anti-phosphopeptide antibodies, and is the standard approach in the field. *See* Polakiewicz Declaration at ¶¶9-11; *see also* Czernik, *supra.* and other references discussed. The number of successful scientific publications reporting production of anti-peptide antibodies, including phospho-antibodies, is innumerable. *See* Polakiewicz Declaration at ¶10. Applicants' specification teaches, in detail, to how to produce the claimed antibodies by largely following the standard anti-peptide production technique, but with the novel modification of using a degenerate peptide library, rather than a single-peptide antigen, to immunize the animal. *See* Polakiewicz Declaration at ¶10. Thus, the cited failure of Heffetz, discussed in the Background section, is *not* indicative of the predictability of the particular approach employed by the inventors, much less of the entire art of antibody production. The invention, in fact, solves the limitations and shortcomings of the prior art approaches, and provides a novel class of antibodies previously not available. *See* Polakiewicz Declaration at ¶20.

In summary, the Examiner has erred by making an unsupportable assertion that the field of antibody production, to which the invention relates, is unpredictable. This assertion goes against the evidence of record in this case, including the USPTO's and Federal Circuit's recognition of the mature, advanced, and predictable nature of this art. The Examiner has also erred by failing to consider all factors, including maturity of the art and known correlation between structure and function, relevant to establishing possession of an invention. Since one of skill in this mature and highly knowledgeable art would recognize, from the description provided in the specification, that the inventors were in possession of the claimed genus of antibodies, the present rejection of claims 28-33 is improper, and should be withdrawn.

C. The Specification Describes Sufficient Identifying Characteristics of the Claimed Genus of Antibodies to Establish Possession to those of Skill in the Relevant Art.

Possession of an invention may be shown in a variety of ways, including – but not requiring all of – actual reduction to practice, or by drawings or structural chemical formulas, or by describing distinguishing identifying characteristics of the claimed invention. *See* MPEP §2163(I), *citing, e.g. Eli Lilly*, 119 F.3d at 1568. All that is required to satisfy the written description requirement is that one of skill in the relevant art, reading the specification in view of what is well known and understood in the art, recognizes that the inventors invented what is now claimed. In mature arts with a high level of skill and knowledge, as is the case with antibody production, characterization, and use, the specificity of disclosure necessary to establish possession will be less than that required for immature arts with low knowledge. *See* MPEP 2163(II)(A)(2), *citing Hybritech*, 802 F.2d at 1379.

"Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed'." *See* MPEP §2163(I), *citing Enzo Biochem* 296 F.3d 1316 (Fed. Cir. 2002). As the Federal Circuit has noted, "an inventor is not required to describe every detail of his invention. An applicant's disclosure obligation varies according to the art to which the invention pertains." *Hayes Microcomputer*, 982 F.2d at 1534-35, *cited in* MPEP §2163(II)(A)(3).

In other words, an applicant is only required to describe those features, limitations, and attributes of the invention *that would be understood by those of skill in the art of the invention* as establishing possession of it. The description required for one type of biomolecule, such as an antibody, will therefore be different from that required for a different type of biomolecule, such as a DNA sequence. Indeed, the Federal Circuit has stated:

> "Examples of identifying characteristics [of biomolecules] include a sequence, structure, *binding affinity*, *binding specificity*, molecular weight, and length. Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics can demonstrate the requisite possession. For example, unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activity, *or antibody cross reactivity may be sufficient to show possession of the claimed invention to one of skill in the art.*" *See Lockwood*, 107 F.3d at 1572 (emphasis added), discussed in MPEP §2163(II)(A)(3).

The MPEP provides a similar instruction by stating that, while one skilled in the art of gene isolation may be able to recognize possession of the gene by a description of its restriction map, the same artisan might not recognize possession simply because the gene is described as being capable of digestion by a nuclease. See MPEP §2163(II)(A)(3). In short, an antibody must be described by characteristics understood by those skilled in antibody production and use, and such characteristics will be different than those used to describe a gene.

Here, the presently claimed invention is a genus of antibodies that are characterized by their binding specificity (to a recurring, phosphorylated kinase consensus substrate motif or protein-protein binding motif consisting of up to four invariant amino acids, one or more phospho-amino acids, and optionally, one or more variable/degenerate positions) and context-independent binding capability (binding the motif for which it is specific in multiple different proteins in which it recurs). Antibody production and characterization is a mature art, where the level of skill and knowledge is high. *See supra.*

Again, the USPTO's own Written Description Guidelines acknowledge the "the routine art-recognized method of making antibodies to fully characterized antigens, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." *See* PTO Guidelines, *supra.* at p. 59-60.

Given the well-known structure of antibodies, their binding functions, and the recognized correlation between structure and function of antibodies, those of skill in this art recognize possession of an antibody by a description of its binding specificity and characteristics (*not* by a diagram of its structure or by its sequence). *See* Polakiewicz Declaration at ¶23.[8] As earlier discussed, the Federal Circuit in *Enzo Biochem* acknowledged as much in contrasting the sequence requirements for DNA claims with the requirements for antibody claims:

> "For example, the PTO would find compliance [with the written description requirement] for a claim to an isolated antibody capable of binding to antigen X, *notwithstanding the functional definition of the antibody*, in light of the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that antibody technology is well developed and mature." *Enzo Biochem*, 296 F.3d 1316, *citing the* USPTO Written Description Guidelines.

The *Enzo* court then went on to state its agreement with, and adoption of, the PTO's approach to assessing adequate written description in well developed arts with a high level of skill, where a known correlation between structure and function exists, such as with antibody production. *See also Hybritech*, 802 F.2d 1367.

Applicants have, therefore, described sufficient identifying characteristics of the claimed type of novel antibody in terms that are recognized as establishing possession to those of skill in this advanced art. The presently claimed subject matter in its broadest sense is a genus of antibodies (see claim 28). To establish possession of this genus, Applicants must sufficiently describe identifying characteristics of a

---

[8] The Examiner's reliance, therefore, on *Vas-Cath* is misplaced. In *Vas-Cath*, the Federal Circuit merely stated that in some arts, possession can be shown entirely by drawings, while in other arts, drawings alone would not suffice. In no way did *Vas-Cath* hold that drawings are *always* required in all technologies. Reliance on *Fiers v. Revel* and *Eli Lilly* is also misplaced. In both *Fiers* and *Eli Lilly*, the Federal Circuit merely stated that a claim to a DNA (a chemical substance) requires a description of its chemical sequence. In no way did the Federal Circuit mandate that recitation of sequence is *always* required for all inventions. To the contrary, it clearly stated that is not the case in other decisions like *Enzo Biochem* and *Lockwood*, discussed above, and stated that functional characteristics may indeed suffice in mature arts where the structure-function correlation is well recognized (as with antibodies). Drawings are not necessary (and arguably not relevant) to establish possession of an antibody since those of skill in this mature art recognize possession by binding characteristics, not by structure or sequence of the antibody itself. *See Enzo Biochem*, *Lockwood*, and *Hybritech; see also* Polakiewicz Declaration at ¶23.

representative number of species within the claimed genus. As the MPEP instructs, possession of a genus may be satisfied through:

> "description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus." MPEP §2163(II)(A)(3), *citing Eli Lilly*, 119 F.3d at 1568 (emphasis added).

In other words, possession is satisfied by *any combination* of identifying characteristics sufficient *in the eyes of those of skill in the relevant art*. What constitutes a "representative number of species" depends on the nature of the claimed subject matter, and whether there is substantial variation within the genus. Again, the assessment is made from the standpoint of one of skill in the relevant art, considering the level of knowledge in the art. In mature arts with a high level of knowledge and skill and reasonable predictability, one or a few species may adequate represent a genus. *See* MPEP §2163(II)(A)(3), *citing In re Rasmussen*, 650 F.2d 1212, 1214 (CCPA 1981). On the other hand, if a genus embraces widely variant species and relates to an unpredictable art, description of a single species will not support a genus claim. *See Eli Lilly* (description of a *single* DNA sequence did not support a genus encompassing all possible DNA sequences encoding the same protein because *common features possessed by members of claimed genus not described*, thus difficult to predicting exact sequences that would encode the same protein); *compare Enzo Biochem* (in holding that not all functional descriptions of DNA fail, noting that three deposited DNA probes may constitute a representative number of species within a genus because common features of members described).

In the present case, Applicants have established possession of the claimed genus by describing the actual reduction to practice of *six* exemplary species that are representative of the variation within the genus *and by* describing sufficient identifying characteristics that are common to members of the claimed genus. As earlier discussed, both the USPTO and Federal Circuit have recognized the high level of skill and knowledge in antibody production and the mature state of this art. The structure and function of antibodies, and the correlation between the two, is known and established. Against this backdrop, Applicants' specification describes in detail the identifying characteristics of both binding specificity and context-independence that are common to antibodies within the claimed genus. The antibodies specifically bind short, recurring, kinase consensus substrate motifs or protein-protein binding motifs that

include one or more phosphorylated amino acid(s), the typical structure of which is described in the specification. *See, e.g.* Specification at p. 7, line 16 to p. 8, line 14; p. 19, line 21 to p. 20, line 26; p. 1, line 15, to p. 2, line 18, and Examples II-IV, VI-VIII. The characteristics and structure of such motifs, which recur in multiple different proteins and serve as conserved or "consensus" phosphorylation sequences for a particular enzyme (*e.g.* a MAPK kinase) or as conserved protein-protein binding sites (*e.g.* a 14-3-3 binding site), have been well described and are known to those of familiar with signal transduction research, to which the invention relates. *See* Polakiewicz Declaration at ¶14, *citing* Kemp *et al., Trends in Biochem. Sci. 15:* 342-46 (1990); Kemp *et al., Methods in Enzymology 200:* 62-81 (1991); Songyang *et al., Mol. Cell Biol. 16:* 6486-493 (1996); al-Obeidi *et al., Biopolymers 47:* 197-223 (1998); L. Cantley, overview in Cell Signaling Technology, Inc. 2000-2001 Catalogue at p. 198; Tony Pawson, *Nature 373:* 573-580 (1995).

Those of skill in this art appreciate the structure of such recurring motifs, which typically comprise up to four invariant amino acids, include one or more phosphorylated amino acids, and often (but not always) comprise one or more variable (degenerate) amino acid positions. *See* Polakiewicz Declaration at ¶16. The six exemplary species of antibodies reduced to practice in the Examples of the specification each bind to a motif that is representative of the variation in kinase consensus substrate motifs and protein-protein binding motifs. *See* Polakiewicz Declaration at ¶16, 18, and Kemp *et al., supra; al-Obeidi et al. supra.* Specifically, the production of antibodies against the following exemplary kinase consensus substrate and/or protein-protein binding motifs are described: PXS*P (MAPK consensus substrate site), RSXS*XP (14-3-3 binding site), PXT*PXR (CDK consensus substrate site), RXRXXT* (AKT consensus substrate site), RRXT* (PKA consensus substrate site), and [F/Y][T/S]* or [T/S]*F (Bulky-ring directed kinase consensus substrate site). Clearly, the inventors had possession of these representative antibody species since they were actually reduced to practice. Moreover, these exemplary species, which bind phosphorylated kinase consensus substrate or protein-protein binding motifs ranging from two to six residues in length, including from one to four invariant residues, and including from zero to four variable (X) positions, are representative of the variation of motif species within the genus. *See, e.g.* Kemp *et al* (1991) (Table II), Al-Obeidi *et al.,* (Table III), discussed in Polakiewicz Declaration at ¶16. Standard methods for determining kinase consensus and protein-protein binding motifs have also been well described and are known in the art. *See, e.g.*, Cantley *et al.*, U.S. Patent No. 5,532,167, "Substrate Specificity of Protein Kinases," Issued July 2, 1996; Yaffe *et al., Nature Biotech. 19:* 348-353 (2001); Tegge *et al.; Biochemistry 34(33):* 10569-77 (1995); Tegge *et al., Methods Mol. Biol. 87:* 99-106 (1998); all discussed in Polakiewicz Declaration at ¶14.

The context-independent functional characteristic of antibodies within the claimed genus (*i.e.*

their ability to specifically bind their target motif in multiple different peptides/proteins in which the motif recurs) is also described throughout the specification, including the Examples. *See, e.g.* p. 8, lines 16-22; p. 19, line 21 to p. 26, line 24 generally; p. 6, line 5 to p.7, line 12; and Examples I-VIII. This characteristic feature of antibodies within the claimed genus is appreciated and understood by those of skill in the art. *See* Polakiewicz Declaration at ¶18. Applicants' description of the identifying characteristics of antibodies within the claimed genus, and of the representative species reduced to practice in the specification, sufficiently indicate, to those of skill in the mature art of antibody production (where structure and function of antibodies are well characterized), possession of the claimed genus of antibodies. *See* Polakiewicz Declaration at ¶17. The law does not require that Applicant go so far as to describe each and every species within the claimed genus. [9] Those of skill in the art can readily distinguish antibodies within the genus of antibodies claimed by the inventors from antibodies outside the genus. *See* Polakiewicz Declaration at ¶18; *see also Lilly, Enzo Biochem, supra.*

Accordingly, Applicants have, in providing a detailed description of the binding specificity and characteristics of the claimed genus of antibodies, described sufficient identifying characteristics of the genus *to establish possession in the eyes of those skilled in the mature art of antibody production, characterization, and use.* Applicant has satisfied the written description requirement because the skilled artisan would recognize, in Applicants' disclosure, the invention and possession of a class of antibodies characterized by its unique features of binding specificity (recurring, phosphorylated kinase consensus substrate motifs and protein-protein binding motifs) and context-independence (ability to bind the motif in multiple different proteins in which it recurs), as well as how the features of the claimed class of antibody differs from prior art antibodies outside the genus. Therefore, the maintained rejection of claims 28-32 is improper, and should be withdrawn.[10]

D. The Examiner has Erred by Failing to Establish a Prima Facie Showing of Insufficient Written Description.

There is *a strong presumption* that an adequate written description of the claimed invention is present when the application is filed. *See* MPEP §2163(A), *citing In re Wertheim* (CCPA 1976). *The initial burden is on the Examiner* to present *evidence or reasons* why a person skilled in the art would not

---

[9] The Federal Circuit (and MPEP) has made clear that possession of genus does not require a written description so detailed that it would provide explicit support for every species within the genus. *See, e.g. Utter v. Hiraga*, 845 F.2d 993 (Fed. Cir. 1988); *see also* MPEP §2163(II)(A)(3).

[10] Of note, the inventors obviously had possession of the six exemplary antibodies that were actually reduced to practice and described in detail in Examples II-IV and VI-VIII. Therefore, the rejection of claim 29, a dependent claim drawn to those preferred and exemplary antibodies, is clearly improper and should be withdrawn.

recognize that an applicant is in possession of the claimed invention. *See* MPEP §2163(II)[A]; MPEP §2163.04. An Examiner must carry this burden by a preponderance of the evidence, and must set forth express findings of fact to support an allegation of inadequate written description. *See Id.* Again, the MPEP stipulates that a general allegation of "unpredictability in the art" is *not* a sufficient reason to make or support a written description rejection. *See Id.*

In the present case, the Examiner has failed to provide *any* evidence or facts (much less a preponderance) supporting why one of ordinary skill in the mature and predictable art of antibodies, their production, characterization, and use would fail to recognize possession of the claimed genus of antibodies as of the filing date of the application. No express findings of *fact* have been presented. No evidence has been adduced to support the cursory allegation that the six exemplary species actually reduced-to-practice are not representative of the claimed genus. Indeed, the required initial showing is not possible based on the evidence of record in this case, including the USPTO's and Federal Circuit's recognition of the high level of knowledge and skill in this mature art.

Accordingly, the Examiner has erred by failing to establish the required *prima facie* showing of inadequate written description. The maintained rejection of claims 28-33 is therefore improper, and should be withdrawn.

§102 REJECTIONS

(I). The Examiner has maintained the rejection of claims 27-33 under 35 U.S.C. §102(e) as allegedly being anticipated by Tani *et al.* (U.S. Patent No. 6,001,580 issued December 14, 1999) (hereinafter the " '580 patent"). The Examiner asserts that the anti-ERK1/ERK2 phosphorylation site-specific antibody disclosed in the '580 patent meets all the limitations of the presently claimed genus of antibodies. Applicants disagree, as the antibody disclosed in the '580 patent is no more than a traditional site-specific antibody, which does *not* possess the binding specificity or characteristics of the motif-specific, context-independent antibodies of presently claimed.

It is a bright-line rule that a cited reference *only* anticipates a claimed invention if the reference discloses *each and every element or limitation* of the claimed subject matter; the so-called "all elements" rule. *See* MPEP §706.02; MPEP §2131, *citing Verdegaal Bros. v. Union Oil of Cal.* (Fed. Cir. 1987). The antibody disclosed in the '580 patent fails to meet this test because it does not teach each and every element or limitation of the claimed subject matter.

Motif-Specific, Context-Independent Antibodies are Distinct from Site-Specific Antibodies.

In order to assist the Examiner in better understanding the features of the claimed subject matter (a novel genus of antibodies), Applicants here again briefly summarize and distinguish the binding specificity, characteristics and features of the presently claimed class of antibodies from those of prior art "site-specific" antibodies, which lack these characteristics. *See* Polakiewicz Declaration at ¶12.

As discussed at length in the Background section of the present application, there was, at the time the present application was filed, an unmet need for a new type of antibody that would be capable not only of specifically binding a short, modified (*e.g.* phosphorylated) and recurring sequence motif, but would also be capable of binding it in many different proteins from an organism in which it recurred. Antibodies with such binding characteristics were envisioned to be highly useful and necessary for researching signal transduction pathways, where such short modified, recurring motifs were known to be central to propagation of an intracellular signal among different proteins involved the signaling cascade. *See, e.g,* Background at page 1, lines 6-21. However, antibodies with such binding characteristics were not yet available and, therefore, research efforts had been limited and burdened by the necessity to use many different antibodies each essentially capable of specifically binding only a single protein or phosphorylation site for which they were designed to be specific. Although the production and use of such site-specific antibodies, including phosphorylation-site specific antibodies was well known and developed in the art, the usefulness of these antibodies in signal transduction research remained limited. *See* Polakiewicz Declaration at ¶12.

The present inventors overcame the limitations of prior art site-specific antibodies by providing, for the first time, a novel class of antibodies having the desired binding features of motif-specificity (the ability to specifically bind short, recurring sequences motifs relevant to signal transduction processes) and context-independence (the ability to bind the motif in many different proteins within an organism in which it recurred). Prior art site-specific antibodies produced by the standard anti-peptide production methodologies (such as those disclosed in the '580 and '787 patents cited by the Examiner and discussed below) *do not* have the binding specificity and characteristics of the presently claimed class of antibodies. Rather, site-specific antibodies are typically raised against – and are specific for – unique, longer sequences (or epitopes) that occur in a single protein; such antibodies, therefore, do not specifically bind recurring motifs, such as kinase consensus substrate motifs, and do not specifically bind multiple different proteins that contain such a recurring motif. Accordingly, the binding characteristics and specificity of traditional site-specific antibodies is distinguished from the presently disclosed class of motif-specific, context-independent antibodies. *See* Polakiewicz Declaration at ¶12, 18. The difference in the binding

specificity and characteristics of traditional site-specific antibodies and the motif-specific antibodies of the present invention are visually shown in a diagram attached hereto for the Examiner's convenience.

The powerful and novel class of antibodies provided by the invention enable, for the first time, the ability to simultaneously examine the modification statuses of multiple different signaling proteins (containing a recurring modified motif) from an organism using a single antibody, and are changing the face of signal transduction research. Among such antibodies are the preferred genus of kinase consensus substrate or protein-protein binding motif–specific antibodies presently claimed; unique antibodies, that, until the time of the present invention, were not available.

In stark contrast, the antibody disclosed in the cited '580 patent is merely a traditional site-specific anti-peptide antibody that binds the kinase ERK1, and its homologue ERK2, only when phosphorylated at a particular epitope. This antibody was generated by standard anti-peptide antibody methods (described in Czernik *et al, see supra.*), using a 12 amino acid long synthetic phospho-peptide, His-Thr-Gly-Phe-Leu-Thr*-Glu-Tyr*-Val-Ala-Thr-Arg (*=phosphorylated residue) as an antigen. This sequence corresponds to a unique epitope present in ERK1 kinase (at residues 197-208; see Fig. 6 in '580 patent) and its homologue ERK2 kinase (at residues 180-191; see Fig. 11 in '580 patent). The '580 patent reports that this epitope was specifically chosen because it was known to be identical in both homologues of ERK kinase. *See* '580 patent column 10, lines 50-65; see also Example 6, column 24. The '580 patent does *not* disclose that this epitope recurs in any other proteins than the homologues, ERK1 and ERK2, which are essentially the same protein (it is stated that these two MAP kinase species are highly homologous (84.7%), and have never been shown to be different in either function or activity (*See* '580 patent at column 1, lines 26-34)). The '580 patent does not disclose that the epitope bound by this antibody is a kinase consensus substrate motif or protein-protein binding motif that recurs in other proteins (ERK itself *is* a kinase but the '580 patent does not disclose that the unique ERK phosphorylation site bound by the antibody serves as a consensus substrate motif or protein-protein binding motif recurring in any other proteins; it is not a motif within the meaning of the present specification). *See* Polakiewicz Declaration at ¶25. Further, the '580 patent does *not* disclose that this antibody is capable of binding the epitope against which it was raised in any proteins other than ERK1/2. Accordingly, the site-specific antibody described in the '580 patent is distinct from, and does not have the characteristics and features of, the presently claimed class of motif-specific, context-independent antibodies. *See* Polakiewicz Declaration at ¶24, 25.

Since the '580 patent does not disclose an antibody that meets all limitations of the presently claims, it does not anticipate the subject matter of claims 28-33, and the maintained novelty rejection of

these claims is therefore improper and should be withdrawn.[11]

(II). The Examiner has also maintained the rejection of claims 28-33 under 35 U.S.C. §§102(e) as allegedly being anticipated by Strulovici (U.S. Patent No. 5,759,787, issued June 2, 1998) (hereinafter the " '787 patent"). The Examiner asserts that the anti-GFAP and/or anti-mitotic protein site-specific antibodies disclosed in the '787 meet all limitations of the presently claimed genus of antibodies. Applicants disagree, as the antibodies disclosed in the '787 patent are no more than traditional site-specific antibodies, which do *not* possess the characteristics and features of the motif-specific, context-independent antibodies of claims 28-33.

The '787 patent, like the '580 patent, merely discloses traditional site-specific anti-peptide antibodies, and similarly fails to teach each and every element of the presently claimed subject matter. *See* Polakiewicz Declaration at ¶26, 27. The '787 patent discloses the use of a commercially available anti-GFAP (glial fibrillary acidic protein) antibody, YC10, to detect phosphorylation of a substrate peptide (RRRVTSAARRS, peptide #2) by PKC or PKA kinase; the substrate peptide corresponds to the GFAP epitope (residues 7-12 of GFAP) that is phosphorylated *in vivo* by these kinases. (*See* YC10 Antibody Product Data Sheet (Cat. No. NBA-115), Stressgen Bioreagents, www.stressgen.com). This antibody is a typical site-specific antibody that binds only GFAP when phosphorylated at serine 7, and was produced by standard anti-peptide methods (*see* Czernik) using the following 11 residue peptide as an antigen: R-R-R-V-T-phosphoSer-A-A-R-R-phosphoSer (*See id.*). GFAP is an intermediate-filament, or structural protein, that is a marker of astrocyte cell maturation. (*See id.*) The '787 patent discloses that this antibody binds the target phosphorylation site in GFAP, the protein for which it is intended to be specific (*see* column 6, line 8). The '787 patent does *not* disclose that the epitope bound by the YC10 antibody is a kinase consensus substrate motif or protein-protein binding motif recurring in other proteins (in contrast, it merely states that the GFAP site for which the YC10 antibody is specific is phosphorylatable by a specific kinase (PKA or PKC)). The '787 patent does not disclose that the YC10 antibody is capable of specifically binding the target epitope in any proteins other than GFAP. Accordingly, the YC10 site-specific antibody described in the '787 patent is different from, and does not have the binding specificity, characteristics or features of the presently claimed class of motif-specific, context-independent antibodies. *See* Polakiewicz Declaration at ¶26, 25.

The '787 patent also discloses the use of a monoclonal antibody, MPM-2, that binds a phosphorylated epitope in mitotic proteins, but states that the exact epitope it binds is not known. *See*

[11] Applicants further note that the ERK1/2 site-specific antibody disclosed in the '580 patent in no way anticipates any of the preferred species recited in dependent claim 29.

column 8, lines 49-53. The '787 patent describes using this antibody to detect the phosphorylation, by CAMK II kinase, of a 39 amino acid peptide (peptide #4, see column 6, lines 13-15) that corresponds to a phosphorylation site in RIP (see column 6, line 15), itself a kinase involved in apoptosis (*see* Hsu *et al.* (1996), cited in the '787 patent). The '787 patent does *not* disclose that MPM-2 is specific for a phosphorylated kinase consensus substrate motif or protein-protein binding motif that recurs in any other proteins. Indeed, the '787 points out that the binding specificity of this antibody is unknown. The '787 patent does *not* disclose that the MPM-2 antibody is capable of binding any proteins or peptides other than the 39 amino acid peptide corresponding to a RIP phosphorylation epitope. Accordingly, the site-specific MPM-2 antibody described in the '787 patent is different from, and does not have the characteristics, features, and limitations of, the presently claimed class of motif-specific, context-independent antibodies. *See* Polakiewicz Declaration at ¶27, 25.

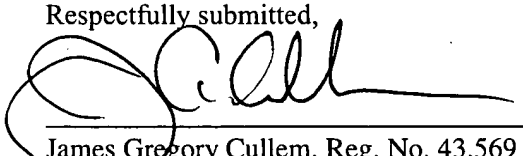
Since the '787 patent does not disclose an antibody that meets all limitations of the present claims it does anticipate the subject matter of claims 27-33, and the maintained novelty rejection of these claims is therefore improper and should be withdrawn.[12]

Conclusion

The pending claims, as amended, are believed to be in condition for immediate allowance. The subject matter of the claims is sufficiently described in the specification and is patentable over the cited references. Applicants submit that all outstanding rejections made by the Examiner have presently been overcome. Accordingly, Applicants respectfully request that the present claims be promptly advanced to allowance and issuance.

If there are any questions regarding these Remarks or Amendments, the Examiner is requested to call the undersigned attorney at the telephone number provided.

Respectfully submitted,



James Gregory Cullem, Reg. No. 43,569
Intellectual Property Counsel
CELL SIGNALING TECHNOLOGY, INC.
166B Cummings Center
Beverly, MA 01915
(978) 867-2311

Dated: May 11, 2004

[12] Applicants further note that the GFAP and mitotic protein site-specific antibodies disclosed in the '787 patent in no way anticipate any of the preferred species recited in claim 29. *See* footnote 11 above.